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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,942	ZAUDERER ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45,48-65 and 69-80* is/are pending in the application.

4a) Of the above claim(s) *21,23,28,36,37,39,42,43,45,48-58,63-65 and 69-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22,24-27,29-35,38,40,41,44 and 59-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/21/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *24 May 2005*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed July 21, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 1-84 were pending. Applicants amended claims 1 and 35 and canceled claims 46, 47, 66-68 and 81-84. Therefore, claims 1-45, 48-65, 69-80 are currently pending. Claims 21, 23, 28, 36, 37, 39, 42, 43, 45, 48-58, 63-65, 69-80 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 1-20, 22, 24-27, 29-35, 38, 40, 41, 44 and 59-62 are examined on the merits in this action.

Restriction

4. Applicants argue that withdrawn claims 48 and 52 should be reconsidered because "[t]he modified phenotype of nonadherence in the present specification and claims is generic to cell death and cell death caused by expression of a suicide gene ... Thus, cells that undergo cell death become nonadherent to the substrate" (e.g., see 7/21/05 Response, page 19). This is not found persuasive. The 35 U.S.C. § 103 rejection below makes clear that Applicants' elected species was found in the art (e.g., see 35 U.S.C. § 103 rejection below, "Zauderer et al. also disclose

modified phenotypes including Applicants' elected "cell death" species ..."). Furthermore, MPEP § 803.02 states that the prior art does not need to be extended to cover all nonelected species that might fall in an overlapping generic and/or subgeneric. See MPEP § 803.02.

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species.*** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

Thus, an overlapping genus that includes "non-adherence" need not be searched (i.e., the subgenus does not necessarily include cell death) and thus another nonelected species would have to be searched, which contradicts MPEP § 803.02.

In addition, the Examiner stated in the 10/7/04 Restriction, "Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on record that this is the case" (e.g., see paragraph 19), which has not been done. In any case, the restriction requirement has already been made final rendering Applicants' arguments moot.

IDS

5. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action (e.g., 9/22/03, 7/1/03, 8/13/02).

Withdrawn Objections/Rejections

6. The Written Description and Enablement rejections under 35 U.S.C. 112, first paragraph are withdrawn in view of Applicants' arguments and/or amendments. The 35 U.S.C. 112, second paragraph rejection denoted "B" is withdrawn in view of Applicants' amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

7. Claims 27, 29, 30, 31, 32, 33, 34, 35, 38, 40, 41 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 27** recites the limitation "the naturally-occurring genome" in the first line. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 27 and all dependent claims are rejected under 35 USC 112, second paragraph.

B. Withdrawn.

Response

8. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been

modified from it original version to more clearly address applicants' newly amended and/or added claims and/or newly amended arguments.

A. Applicants argue that the naturally-occurring genome as recited in the claim refers to a property or feature of the vector and, as a result, the use of the article "the" is appropriate (e.g., see 7/21/05 Response, page 30).

This is not found persuasive for the following reasons:

A. The Examiner fails to see how this distinction renders the lack of antecedent basis less egregious? Applicants' don't previously refer to the naturally-occurring genome. Thus, the claim still lacks antecedent basis.

Accordingly, the 35 U.S.C. 112, second paragraph rejections cited above are hereby maintained.

Claim Rejections - 35 USC § 103

9. Claims 1-20, 22, 24-27, 29-35, 38, 40, 41, 44 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) and Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266) as evidenced by Roitt et al. (Roitt, I.; Brostoff, J.; Male, D. Immunology Sixth Edition. New York: Mosby 2001, page 67) and as also evidenced by Applicants' specification.

For ***claims 1 and 4***, Rowlands et al. (see entire document) teach a method for producing antibodies in vaccinia infected cells including intracellular antibodies that reads on the presently claimed invention (e.g., see Rowlands et al., abstract; see also paragraph bridging pages 15-16 showing production of "intracellular" antibodies i.e., both heavy and light chains found within the cell and thus said host cells are "capable" of expressing intracellular immunoglobulin molecules; see also page 6, paragraph 3). For example, Rowlands et al. teach **[a-d]** the use of a population of mammalian host cells i.e., "eukaryotic" host cells (e.g., see page 4, paragraph 2; see also page 8, paragraph 1) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be

recovered in functional form"). Rowlands et al. further disclose **[d]** permitting expression of said plurality of intracellular immunoglobulin molecules, or fragments thereof, under conditions wherein said modified phenotype can be detected (e.g., see page 5, last paragraph wherein the use of "selectable markers" is disclosed, "The transfer vector contains DNA encoding the light chain and/or the heavy chain of an antibody together with a suitable promoter and the selectable marker will also be under control of a suitable promoter"; see also page 5, second to last paragraph, "Suitable selectable markers ... include ... guanine phosphoribosyltransferase (gpt) gene which allows ... growth of the infected cells [and thus permits the expression of said immunoglobulin molecules] in the presence of mycophenolic acid [i.e., a modified phenotype, which is detected by cell growth]"). Finally, Rowlands et al. disclose **[e]** recovering the vaccinia virus vectors containing polynucleotides of said first library from those individual host cells which exhibit said modified phenotype (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

For ***claim 9***, Rowlands et al. disclose human and "humanized" antibodies (e.g., see claims 2 and 4; see also page 8, last paragraph, "However, the invention is most preferably applied to the production of human antibodies").

For ***claims 10-17***, Rowlands et al. disclose both heavy and light constant/variable region (e.g., see page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains"; see also pages 11-12, Example 1, especially page 12, paragraph 1; see also page 16, Example 5). Rowlands et al. do not explicitly

state that lambda or kappa light chains are employed, but the examiner contends that this would be immediately envisioned in accordance with *In re Schauman*.

In *In re Schauman*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), claims to a specific compound were anticipated because the prior art taught a generic formula embracing a limited number of compounds closely related to each other in structure and function. Here, Rowlands et al. disclose a generic claim drawn to a light chain antibody that contains only two possible structurally related species (i.e., kappa and lambda chains) and, as a result, a person of skill in the art would immediately envision these possibilities.

In the alternative, the Examiner contends that Rowlands et al. inherently disclose the lambda and kappa chains because the light chains of most vertebrates have been shown to exist in only two distinct forms (e.g., see Roitt et al., page 67, column 2, second full paragraph). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 18-20 and 24-27, 29-35, 38***, Rowlands et al. disclose the "eukaryotic" vaccinia poxvirus vector (e.g., see page 13, Example 3). Rowlands et al. do not explicitly state that the vaccinia virus is a linear, double-stranded DNA othopoxvirus vector. However, the Examiner contends that these would be inherent features of the virus as disclosed by Applicants' specification (e.g., specification, page 6, paragraph 13

demonstrating that vaccinia poxvirus is a "eukaryotic" vector; see also pages 6-7; see especially page 63, paragraph 144, "The naturally-occurring vaccinia virus genome is a cross-linked, double stranded linear DNA molecule"; see also page 62, paragraph 142, disclosing vaccinia to be an orthopoxvirus). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 40, 41 and 44***, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter"; see also claim 6 wherein p7.5k, 11k and 19k are disclosed).

The prior art teachings of Rowlands et al. differ from the claimed invention as follows:

For ***claim 1***, Rowlands et al. are deficient in that they do not specifically teach the use of a "library" of first/second polynucleotides.

For ***claims 2-8 and 10-20***, Rowlands et al. do not disclose repetitive steps (f)-(j), (k)-(o) and (p)-(t) for "biopanning" a library including isolating/recovering said

polynucleotides for use in subsequent rounds of biopanning for library "enrichment" of the "focused" libraries associated with the subsequent screening steps.

For ***claim 22***, Rowlands et al. do not disclose an MOI of 1.

For claims ***59-61***, Rowlands et al. do not disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence

However, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al.:

For ***claim 1***, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266). Furthermore, Zauderer et al. also disclose modified phenotypes including Applicants' elected "cell death" species (e.g., see Zauderer et al., page 34, line 14, "Alternatively, recombinant viruses with 'suicide' characteristics may be constructed").

For ***claims 2-8, 10-20***, Zauderer et al. disclose steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity i.e., they use "biopanning" techniques (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure"). Zauderer et al. disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 22***, Zauderer et al. disclose, for example, an MOI = 1 (e.g., see page 86, line 2).

For ***claims 59-61***, Zauderer et al. disclose, for example, the use of histidine tags which represent common heterologous fusion targeting sequences (e.g., see page 33, line 13).

It would have been obvious to one skilled in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular

recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach

several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al.

Response

10. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "... the cited references do not teach or suggest the introduction of two expression libraries into eukaryotic host cells" (e.g., see 7/21/05 Response, page 32).

[2] Applicants argue, "There is nothing in Rowlands, Zauderer, or Waterhouse that would have motivated or suggested to one of ordinary skill in the art the desirability of combining these reference. While Rowlands describes the expression of a single, previously known and identified recombinant antibody using a *vaccinia* virus vector, there is no suggestion provided therein that would have motivated one of ordinary skill in the art to introduce two expression libraries encoding immunoglobulin subunit polypeptides into eukaryotic cells. Furthermore, while Zauderer describes the introduction of a single expression library of tumor, cancer, or infected cell-specific antigens, there is no suggestion to one of ordinary skill in the art that this could be used in conjunction with the Rowlands method" (e.g., 7/21/05 Response, pages 33 and 34).

[3] Applicants argue, "Waterhouse does not even describe eukaryotic host cells ... there is nothing in Waterhouse to suggest to one of ordinary skill in the art to introduce two expression libraries into eukaryotic cells for selecting polynucleotides which encode an immunoglobulin molecule" (e.g., see 7/21/05 Response, page 34).

[4] Applicants argue, "Applicants submit herewith as Exhibit B the Declaration under 35 C.F.R. § 1.132 of Dr. Maurice Zauderer ... [stating] there was no motivation or suggestion for one of ordinary skill in the art to combine Rowlands, Zauderer, or Waterhouse to arrive at the claimed invention because: 1) Rowlands does not teach or suggest introduction of libraries into eukaryotic cells; 2) Zauderer does not teach or suggest introduction into eukaryotic host cells of two expression libraries that separately encode immunoglobulin heavy and light chains; and 3) Waterhouse describes phage display techniques, which one of ordinary skill in the art would not have considered as features that could be extrapolated to eukaryotic systems. See Exhibit B at Paragraph 15" (e.g., see 7/21/05 Response, page 35; see also Exhibit B).

[5] Applicants argue, "One of ordinary skill in the art would not have reasonably expected that the phage display technology described in Waterhouse could be extrapolated to methods of introducing two random expression libraries into eukaryotic host cells ... Given these different vectors and the difference in prokaryotic versus eukaryotic host cells, one of ordinary skill would not have expected any selection methods described in Waterhouse to be useable with vectors that express in eukaryotic hosts because there would be different conditions required for the two systems" (e.g., 7/21/05 Response, page 36, middle paragraph; see also paragraph bridging pages 36 and 37).

[6] Applicants argue, "... one of ordinary skill in the art would not have expected from Zauderer, which discloses introduction of one library into eukaryotic host cells, and Rowlands, which discloses the expression of a previously identified and known antibody in eukaryotic host cells, that two separate libraries could be randomly introduced into eukaryotic host cells to efficiently form a plurality of immunoglobulin ... submitted herewith as Exhibit A is a copy of the Declaration of Dr. Walter J. Storkus ... he did not expect that good antibodies could be selected in eukaryotic cells because ... he thought that there would be limitations on the throughput for screening libraries expressed in eukaryotic cells, and because it was thought that random pairs of immunoglobulin heavy and light chains, when expressed, would not associate properly in the eukaryotic cytoplasm" (e.g., see 7/21/05 Response, pages 37 and 38; see also Exhibit A, especially at paragraph 9).

[7] Applicants argue, that there was a long-felt and unmet need for the technology of the claimed invention because of the drawbacks that are associated with the two prevalent technologies for selecting human antibodies (e.g., see Zauderer Declaration, paragraphs 16 and 17). This long felt need is evidenced by the strategic alliances hat have been formed between Vaccinex, Inc., exclusive licensee of the present invention, and several other companies that are interested in using the claimed invention" (e.g., see exhibits B2-B4).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. Applicants have already acknowledged that the combined references teach the use of two libraries (e.g., see 7/21/05 Response, page 32, last paragraph, "Waterhouse discloses the introduction ... vectors encoding immunoglobulin heavy and light chain variable region fragments ... and suggests that the system can be used to generate

large combinatorial libraries by providing repertories of heavy [i.e., library number 1] and light chain [i.e., library number 2] fragments").

[2] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265,

column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously). Furthermore, in response to applicant's arguments against the Rowlands reference individually (or in combination with Zauderer), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[3] The Examiner respectfully disagrees. A person of skill in the art (most likely a Ph.D.) working in the field of immunology and/or combinatorial chemistry (i.e., for the purpose of producing antibody and/or antibody libraries) would look to all relevant papers for guidance (e.g., papers encompassing phage display, vaccinia virus, etc.) because the problems encountered are not "unique" to any one system. The advantages obtained from producing large "primary" libraries of heavy and light chains (i.e., two libraries) and the advantages associated with being able to co-select these heavy and light chains in order to produce, for example, antibodies with high affinity are just as applicable to mammalian expression systems as they are to phage display. The products in each case (i.e., the antibodies or antibody libraries) would be the same. Furthermore, Applicants' own specification makes clear that a person of skill in the art would routinely look at a wide variety of expression systems for guidance (e.g., see specification, page 2 and 3, "Previously, three general strategies have been employed to produce immunoglobulin molecules ... In one approach, rodent antibody sequences have been converted into human antibody sequences, by grafting ... An alternative approach, which does not suffer this same limitation, is to screen recombinant human antibody fragments displayed on bacteriophage").

Thus, Applicants' arguments for a per se rule that a person of skill in the art would never combine the teachings of a "phage display" reference with a "vaccinia virus" reference even if both references teach a method for producing antibodies is not persuasive. Both papers deal with the production of antibodies and, as a result, represent analogous art (e.g., see *In re Paulsen* 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem). Furthermore, in response to applicant's arguments against the Waterhouse et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[4] The Declarations under 37 CFR 1.132 filed 7/21/05 are insufficient to overcome the rejection of claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 based upon 35 U.S.C. 103(a) rejections as set forth above because:

"In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion." (e.g., see MPEP § 716.01(c)). Here, Applicants provide no factual evidence. The interest of the expert in the outcome is great (i.e., it's the expert's application at issue). The opposing evidence is strong for the reasons stated in the newly amended rejection above. Finally, the nature of the matter, which Applicants are trying to establish, pertain only to legal conclusions (e.g., no motivation to combine, no reasonable expectation of success, etc.) that have

been set forth in an entirely conclusory manner and thus should be afforded little or no weight (e.g., see *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement").

For example, Dr. Zauderer states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. For example, the claimed invention requires expression of an antibody library using a poxvirus. The Zauderer et al. reference (WO 00/28016), which teaches the expression of protein libraries using a poxvirus, was published on May 18, 2000. There is no evidence that anyone was working on a method to express fully functional antibodies in mammalian cells using the Zauderer et al. reference. Furthermore, even if such evidence did exist, *assuming arguendo*, it would not constitute a long felt need as this paper was published fairly recently. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited reference; they would still be unable to solve the problem. See MPEP § 716.04.

Furthermore, Applicants' arguments are not commensurate in scope with the claimed invention. The Declaration refers only to the system described in the above referenced application and not to the individual claims of the application. As such the declaration does not show that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716. For example, the Zauderer Declaration sets forth, "The claimed invention is directed to method for selecting polynucleotides ... encoding immunoglobulin subunit polypeptides wherein the libraries are constructed in vaccinia virus vectors" (e.g., see Zauderer

Declaration, paragraph 6). However, Applicants' claims are not limited to vaccinia virus vectors (e.g., see newly amended claim 1, which does not even require a "poxvirus" vector because Applicants use the word "if"). Dr. Zauderer also states, no useful antibodies can be selected in immunoglobulin transgenic animals ... once the antigen-specific variable region is isolated from the phage and expressed as an IgG molecule, it often no longer recognizes the target antigen ... the present invention overcomes these problems (e.g., see Zauderer Declaration, paragraphs 8-10). However, Applicants also make clear that the claimed invention is not limited to an "efficient" method for the production of "useful" antibodies (e.g., see 7/21/05 Response, page 23, first full paragraph, "... there is no requirement in the claims for a particular titer or recombination efficiency"; see also claim 1, which includes antibody fragments). Thus, there was no long felt need to produce antibodies and/or antibody fragments with low binding affinity and/or specificity as these goals were readily obtainable by other means (e.g., see Zauderer Declaration, paragraph 9, "... once the antigen-specific variable region is isolated from the phage and expressed as an IgG molecule, it often no longer recognizes the target", which implies that sometimes it does recognize the target, which obviates Applicants' long felt need argument; see also Zauderer Declaration, paragraph 8, "In some cases ... no useful antibodies can be selected in immunoglobulin transgenic animals", which implies that in other cases usefully antibodies can be obtained, which again obviates Applicants' long felt need argument). That is, Applicants' claims are not limited to an "efficient" method that produces antibodies with a high degree of selectivity and/or affinity. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

In addition, in response to applicant's arguments against the Rowlands reference individually (i.e., with regard to point 1), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Likewise, in response to applicant's arguments against the Zauderer reference individually (i.e., with regard to point 2), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *Id.* Moreover, in response to applicant's arguments against the Waterhouse et al. reference individually (i.e., with regard to point 3), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *Id.*

[5] The Examiner respectfully disagrees. Obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903-904 [7 USPQ2d at 1681]. Here, Rowlands et al. teach a method for producing antibodies in vaccinia infected "mammalian" cells (e.g., see Rowlands et al. page 4, paragraph 2; see also paragraph bridging pages 7-8). Thus, the conclusion that a person of skill in the art would know how to express an antibody in a "mammalian" cell is reasonable. Zauderer et al. teach how to make and/or use a library of proteins using a vaccinia virus vector like the vaccinia virus vector disclosed by Rowlands (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). Thus, the conclusion that a person of skill

in the art would know how to make and/or use a library of proteins, including antibodies, with a vaccinia virus is reasonable. The Zauderer et al. reference never states or indicates in any way that the use of tri-molecular recombination should somehow be limited to expressing only one particular class of proteins (i.e., everything but Applicants' claimed antibodies). Furthermore, the prokaryotic/eukaryotic distinctions to which Applicants refer are not at issue in this case. The Waterhouse et al. reference is not being relied upon for the purpose to which Applicants allude. The Examiner has never contended that the eukaryotic systems should somehow employ prokaryotic reaction conditions in some sort of hybrid expression system. The Waterhouse et al. reference is simply being relied upon to show that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced. Thus, Applicants' arguments are moot.

[6] The Declarations under 37 CFR 1.132 filed 7/21/05 are insufficient to overcome the rejection of claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 based upon 35 U.S.C. 103(a) rejections as set forth above because:

Applicants' arguments are not commensurate in scope with the claims (e.g., see *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims); see also *In re Tiffin and Erdman*, 171 USPQ 294 (CCPA 1971) and cases cited therein; see also MPEP § 716.02(d). The claims do not require "efficient" introduction of libraries into host cells or the production of "good" antibodies as Dr. Storkus contends. In fact,

Applicants make clear that low efficiency methods that generate poor antibodies are also to be included within the scope of Applicants' claims (e.g., see 12/7/04 Response, page 22, "While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer ... it does not say that methods such as direct ligation or modified homologous recombination cannot be used to generate vaccinia virus expression libraries ... there is no requirement in the claims for a particular titer or recombination efficiency"). Furthermore, there is no requirement that the antibodies associate properly in the "cytoplasm" and any underlying facts to support this contention, which have not bee set forth by Dr. Storkus, have been refuted by the combined teachings of Rowlands et al., Zauderer et al. and Waterhouse et al., which clearly sets forth successful examples of the proper association of heavy and light chains (e.g., see page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). In addition, Applicants' claims are not even limited to antibodies. For example, a claim 1 states that "fragments thereof" may be screened. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

[7] The Declarations under 37 CFR 1.132 filed 7/21/05 are insufficient to overcome the rejection of claims 1-20, 22, 24-27, 29-35, 38, 40, 41, 44 and 59-61based upon 35 U.S.C. 103(a) as set forth above because:

Applicants' arguments are not commensurate in scope with the claims (e.g., see *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims); see also *In re Tiffin and Erdman*, 171 USPQ 294 (CCPA 1971) and cases cited therein; see also MPEP § 716). In the present case, Dr. Zauderer states, "The transgenic animal technology ... tends to produce antibodies that do not have useful activity. Phage display technology ... results in antibodies that, once removed from the context of the fusion protein, lose the ability to specifically recognize target antigen [which are limitations that are presumably overcome by the claimed invention]" (e.g., see Dr. Zauderer's Declaration, paragraph 16). However, "antibodies" with "useful" activity that recognize a specific target protein are not required by the claims. In fact, Applicants make clear that low efficiency methods that generate poor antibodies also fall within the scope of Applicants' claims (e.g., see 7/21/05 Response, page 23, "While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer ... it does not say that methods such as direct ligation or modified homologous recombination cannot be used to generate vaccinia virus expression libraries ... there is no requirement in the claims for a particular titer or recombination efficiency"). For example, Exhibit B3, sets forth, "Vaccinex's innovative library-based antibody discovery technology ... will offer true value to customers by producing substantial quantities of high quality, fully functional human monoclonal antibodies that would have been difficult [i.e., not impossible] to identify with other systems." Thus, Exhibit B3 makes clear that Applicants'

licensees are only bargaining for Vaccinex's "efficient" methods for producing library-based antibodies, which is not commensurate in scope with the current claims. In addition, Applicants' claims are not even limited to antibodies. For example, claim 1 states that "fragments" may be screened.

Exhibits B2-B4 only serve to highlight this deficiency. For example, Exhibit B2 sets forth, "Vaccinex's technology offers the potential to directly generate fully functional antibodies against difficult targets such as homologous proteins and multi-pass membrane receptors" and Gilles Alberici, CEO of OPi, is quoted as saying, "We are excited about this collaboration with Vaccinex ... Vaccinex's innovative antibody discovery technology will enable use to make a technological leap to develop new fully human antibodies aiming at treating haematological diseases" (e.g., see Exhibit B2, page 1 of 2). However, the Examiner notes that the claims are not limited to "fully functional antibodies" (e.g., see above wherein Applicants' claims, for example, read on "fragments" thereof). In addition, Applicants claims are not limited to antibodies that bind "difficult targets" for treating haematological diseases. In addition, Applicants' claims are not limited to antibodies with "useful" activity or even to antibodies that bind to a target molecule at all. Likewise, Exhibit B3 sets forth, "Vaccinex's innovative library-based antibody discovery technology ... will offer true value to customers by producing substantial quantities of high quality, fully functional human monoclonal antibodies that would have been difficult to identify by other systems." Again, Applicants' claims are not limited to "high quality, fully functional human monoclonal antibodies" (e.g., see above). Furthermore, Exhibit B4 sets forth, "The collaboration combined Vaccinex's capabilities to discover fully human monoclonal antibodies using its proprietary anti-body discovery technology ... Vaccinex

... has developed the only library-based antibody discovery platform capable of directly expressing bivalent, fully human antibodies in mammalian cells." Again, Applicants' claims are not limited to "bivalent, monoclonal fully human antibodies" (e.g., see above). In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

In addition, Applicants have not established a nexus between the claimed invention and the licenses (e.g., see *In re GPAC Inc.* (CAFC) 35 USPQ2d 1116 (6/20/1995), "Licenses taken under the patent in suit may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate 'a nexus between the merits of the invention and the licenses of record.' Stratoflex, 713 F.2d at 1539, 218 USPQ at 879; see Demaco, 851 F.2d at 1392, 7 USPQ2d at 1226."). For example, Exhibits B2-B4 do not mention the use of a poxvirus vector (claim 31), vaccinia virus (claim 34), constitutive promoter (e.g., see claim 41), etc. Thus, it is not clear whether the expression systems to which exhibits B2-B4 refer represent the currently claimed methods.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

11. Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) and Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266) and Marasco (Marasco, W. A. "Intrabodies: turning the

humoral immune system outside in for intracellular immunization" *Gene Therapy* **1994**, *4*, 11-15) as evidenced by Roitt et al. (Roitt, I.; Brostoff, J.; Male, D. Immunology Sixth Edition. New York: Mosby 2001, page 67) and as also evidenced by Applicants' specification.

For ***claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61***, Rowlands et al. and Zauderer et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61.

The prior art teaching of Rowlands et al. and Zauderer et al. differs from the claimed invention as follows:

For ***claim 62***, the combined prior art teachings of Rowlands et al. and Zauderer et al. differ from the claimed invention by not reciting the use of targeting sequences capable of localizing said intracellular immunglobulin molecule.

However, Marasco teaches the following limitations that are deficient in the combined teachings of Rowlands et al. and Zauderer et al.:

For ***claim 62***, Marasco (see entire document) teaches, for example, localization in the endoplasmic reticulum using a KDEL-tagged sFv intrabody (e.g., see Marasco, page 12,).

It would have been obvious to one skilled in the art at the time the invention was filed to screen the libraries of antibodies disclosed by the combined teachings of Rowlands et al. and Zauderer et al. using intracellularly expressed and/or localized antibodies like the KDEL-tagged sFV disclosed by Marasco because Marasco explicitly states that such "intrabodies" represent a "... powerful new family of protein molecules

that have potential application in the gene therapy of a number of human diseases" (e.g., see Marasco, page 11, column 2, paragraph 1; see also abstract wherein cancer and infectious diseases are disclosed). Furthermore, one of ordinary skill in the art would have been motivated to use intracellular expression of antibodies because, for example, they would allow for the down-regulation of growth factor receptors like interleukin-2 (e.g., see page 12, column 1), provide for a defense against tumors (e.g., see page 12, column 2), modulate enzyme function (e.g., see page 12, column 1), treat cancer and or other infectious diseases (e.g., see abstract), inactivate cytosolic oncoproteins (e.g., see page 13, column 1), inhibit virus replication (e.g., see page 13, column 2), etc. Finally, one of ordinary skill in the art would have reasonably expected to be successful because Marasco teaches that "the creation of large human immunoglobulin libraries [like the in vitro libraries disclosed by the combined teachings of Rowlands et al. and Zauderer et al.] ... has allowed investigators to bypass in vivo immunization and produce high-affinity human antibodies to human proteins" (see Marasco, page 11, Introduction; see also abstract, "Recent advances in antibody engineering have now allowed the genes encoding antibodies to be manipulated so that the antigen binding domain can be expressed intracellularly").

Response

12. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified

from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "... as set forth above ... there was no motivation to combine Rowlands and Zauderer, and no reasonable expectation of success" (e.g., see 7/21/05 Response, page 39, especially last full paragraph).

[2] Applicants argue, "While the Examiner lists several potential uses of intrabodies as set forth in Marasco, none of them are for methods of selecting polynucleotides encoding intracellular immunoglobulins from first and second expression libraries as in the present invention" (e.g., see 7/21/05 Response, page 40, paragraph 1).

[3] Applicants argue, "there is no suggestion that Marasco could be combined ... Zauderer ... [or] Rowlands to arrive at the present invention" (e.g., see 7/21/05 Response, page 40, paragraph 1)

[4] Applicants argue, "... the phage display technique reference by Marasco involves filamentous bacteriophage vectors and bacterial hosts and, therefore, is not like in vitro libraries that the Examiner alleges are taught by the combined teachings of Rowlands and Zauderer" (e.g., see 7/21/05 Response, pages 40 and 41).

This is not found persuasive for the following reasons:

[1] The Examiner contends that to the extent that Applicants are simply repeating their previous arguments, those points were adequately addressed in those sections, which are incorporated in their entirety herein by reference (e.g., see above).

[2] In response to applicant's arguments against the Marasco reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based

on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[3] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to use intracellular expression of antibodies because, for example, they would allow for the down-regulation of growth factor receptors like interleukin-2 (e.g., see page 12, column 1), provide for a defense against tumors (e.g., see page 12, column 2), modulate enzyme function (e.g., see page 12, column 1), treat cancer and or other infectious diseases (e.g., see abstract), inactivate cytosolic oncoproteins (e.g., see page 13, column 1), inhibit virus replication (e.g., see page 13, column 2), etc.

[4] The Examiner respectfully disagrees. Both papers deal with the production of antibodies and, as a result, represent analogous art (e.g., see *In re Paulsen* 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem). The problems and/or advantages associated with producing intracellular antrabodies (e.g., down-regulation of growth factor receptors like interleukin-2 (e.g., see page 12, column 1), provide for a defense against tumors (e.g., see page 12, column 2), modulate

enzyme function (e.g., see page 12, column 1), etc.) are just as applicable to phage display as they are to mammalian expression. Thus, the Marasco/Rowlands/Zauderer distinctions to which Applicants refer are not at issue in this case. The Marasco et al. reference is not being relied upon for the purpose to which Applicants allude. The Examiner has never contended that the eukaryotic systems should somehow employ prokaryotic reaction conditions in some sort of hybrid expression system. The Marasco et al. reference is simply being relied upon to show that a person would be motivated to produce a library of intracellular antibodies regardless of how those antibodies are produced. Thus, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

13. Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 84-122 and 127-131 of U.S. Patent Application Serial No. 09/984,456 (referred to herein as '456) and Marasco (Marasco, W. A. "Intrabodies: turning the humoral immune system outside in for intracellular immunization" *Gene Therapy* **1994**, *4*, 11-15).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 84-122 and 127-131 '456 recite a method for selecting polynucleotides which encode immunoglobulin molecules which is essentially the same as that disclosed by claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 in the present application (e.g., both methods disclose eukaryotic host cells, a first and second library of polynucleotides encoding immunglobulin light/heavy chain constant/variable regions, permitting expression of said immunoglobulin molecules, contacting the molecules with an antigen, recovering the polynucleotides that encode for immunoglobulins that bind to said antigens, etc). The method of claims '456 differ from the present application in that they claim "extracellular" as opposed to "intracellular" expression as currently claimed (e.g., "signal" sequences are claimed in '456).

However, Marasco teaches the use of "intracellular" expression and localization of antibodies for screening and pharmaceutical applications (e.g., see Marasco, abstract and Introduction).

Thus, it would have been obvious to modify the method of claims 84-122 and 127-131 of '456 such that "intracellular" expression and/or localization occurs because Marasco teaches that "extracellular" expression may be obtained within Applicants' preferred "phage" vectors (e.g., see claim 18 wherein a eukaryotic virus vector is disclosed; see also specification, page 54, paragraph 123 where Applicants define "vectors" to any standard vector which allows expression in eukaryotic cells may be used [including] ... phage"; compare to Marasco, Introduction, "Using these tools, the creation of large human immunoglobulin libraries from naive individuals has been achieved and when combined with phage display technology, has allowed investigators to bypass in

vivo immunization and produce high-affinity human antibodies to human proteins") (emphasis added). Furthermore, one of ordinary skill in the art would have been motivated to use intracellular expression and/or localization of antibodies because, for example, they would allow for the down-regulation of growth factor receptors like interleukin-2 (e.g., see page 12, column 1), provide for a defense against tumors (e.g., see page 12, column 2), modulate enzyme function (e.g., see page 12, column 1), treat cancer and or other infectious diseases (e.g., see abstract), inactivate cytosolic oncoproteins (e.g., see page 13, column 1), inhibit virus replication (e.g., see page 13, column 2), etc. Finally, one of ordinary skill in the art would have reasonably expected to be successful because Marasco teaches that "the creation of large human immunoglobulin libraries [like the in vitro libraries disclosed by the combined teachings of Rowlands et al. and Zauderer et al.] ... has allowed investigators to bypass in vivo immunization and produce high-affinity human antibodies to human proteins" (see Marasco, page 11, Introduction; see also abstract, "Recent advances in antibody engineering have now allowed the genes encoding antibodies to be manipulated so that the antigen binding domain can be expressed intracellularly").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-133 of U.S. Patent Application Serial No. 10/465,808 (referred to herein as '808) and

Marasco (Marasco, W. A. "Intrabodies: turning the humoral immune system outside in for intracellular immunization" *Gene Therapy* **1994**, *4*, 11-15).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 46-133 of '808 recite a method for selecting polynucleotides which encode immunoglobulin molecules which is essentially the same as that disclosed by claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 in the present application (e.g., both methods disclose eukaryotic host cells, a first and second library of polynucleotides encoding immunglobulin light/heavy chain constant/variable regions, permitting expression of said immunoglobulin molecules, contacting the molecules with an antigen, recovering the polynucleotides that encode for immunoglobulins that bind to said antigens, etc). The method of claims '808 differ from the present application in that they claim "extracellular" as opposed to "intracellular" expression as currently claimed (e.g., "signal" sequences are claimed in '808).

However, Marasco teaches the use of "intracellular" expression and localization of antibodies for screening and pharmaceutical applications (e.g., see Marasco, abstract and Introduction).

Thus, it would have been obvious to modify the method of claims 46-133 of '808 such that "intracellular" expression and/or localization occurs because Marasco teaches that "extracellular" expression may be obtained within Applicants' claimed "phage" vectors (e.g., see claim 18 wherein a eukaryotic virus vector is disclosed; see also specification, page 54, paragraph 123 where Applicants define "vectors" to any standard vector which allows expression in eukaryotic cells may be used [including] ... phage"; compare to Marasco, Introduction, "Using these tools, the creation of large human immunoglobulin libraries from naive individuals has been achieved and when combined with phage display technology, has allowed investigators to bypass in vivo immunization and produce high-affinity human antibodies to human proteins") (emphasis added). Furthermore, one of ordinary skill in the art would have been motivated to use intracellular expression and/or localization of antibodies because, for example, they would allow for the down-regulation of growth factor receptors like interleukin-2 (e.g., see page 12, column 1), provide for a defense against tumors (e.g., see page 12, column 2), modulate enzyme function (e.g., see page 12, column 1), treat cancer and or other infectious diseases (e.g., see abstract), inactivate cytosolic oncoproteins (e.g., see page 13, column 1), inhibit virus replication (e.g., see page 13, column 2), etc. Finally, one of ordinary skill in the art would have reasonably expected to be successful because Marasco teaches that "the creation of large human immunoglobulin libraries [like the in vitro libraries disclosed by the combined teachings of Rowlands et al. and Zauderer et al.] ... has allowed investigators to bypass in vivo immunization and produce high-affinity human antibodies to human proteins" (see Marasco, page 11, Introduction; see also

abstract, "Recent advances in antibody engineering have now allowed the genes encoding antibodies to be manipulated so that the antigen binding domain can be expressed intracellularly").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response

15. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "... that this rejection [for '456 and also the '808 application] be held in abeyance until such time as otherwise patentable subject matter has been identified ... At that time, Applicants will consider filing a terminal disclaimer" (e.g., see 7/21/05 Response, page 41 and 42).

This is not found persuasive for the following reasons:

The provisional rejection will not be held in abeyance (e.g., see MPEP § 804 B. Between Copending Applications—Provisional Rejections, "The 'provisional' double patenting rejection *should continue to be made by the examiner* in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications.").

Accordingly, the double patenting rejections cited above are hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
October 21, 2005

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600